Inheritance of Myotonic Discharges in American Quarter Horses and the Relationship to Hyperkalemic Periodic Paralysis

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ABSTRACT

Electromyography (EMG) was used to detect myotonic discharges in Quarter Horse breeding stock and to follow the results of mating horses with hyperkalemic periodic paralysis (HPP). The studies were performed on two brood mare farms. A total of six breeding stock showed myotonic discharges and 15 were nonmyotonic. Myotonic discharges were seen in five of six horses belonging to the blood line previously implicated as being predisposed to HPP. Two of these horses had shown clinical signs of HPP. Only one of 15 breeding horses unrelated to the HPP predisposed blood line showed myotonic discharges. When both parents were nonmyotonic on EMG then the F_1 generation (n = 6) were also nonmyotonic. When a stallion with HPP and myotonic discharges was mated to eight nonmyotonic mares over a six year period half the animals of the F_1 generation (n = 25) showed myotonic discharges. When both parents showed myotonic discharges four F_1 offspring were myotonic and two were nonmyotonic on EMG testing. There was no evidence of sex linkage. The results are consistent with an autosomal dominant mode of inheritance. Hyperkalemic periodic paralysis and myotonic discharges on EMG may be different manifestations of the same underlying defect.

RÉSUMÉ

L'électromyographie (EMG) a été utilisée pour détecter des décharges myotoniques chez des chevaux de race Quarter Horse, ainsi que pour suivre les résultats des croisements entre des chevaux atteints de paralysie périodique hyperkaliémique (PPH). Les études ont été effectuées dans deux fermes d'élevage. Un total de six reproducteurs présentaient des décharges myotoniques, alors que 15 n'en présentaient pas. Les décharges myotoniques ont été observées chez cinq des six chevaux appartenant à la lignée génétique reconnue comme prédisposée à PPH. Deux de ces chevaux ont démontré des signes cliniques de PPH. Seulement un des 15 reproducteurs non-apparentés avec les chevaux génétiquement prédisposés au PPH, a démontré des décharges myotoniques. Lorsque les deux parents étaient non-myotoniques à l'EMG les animaux de la première génération ou F1 (n = 6) étaient aussi non-myotoniques. Lorsque, durant une période de six ans, un étalon avec PPH et décharges myotoniques, était accouplé avec huit juments non-myotoniques, la moitié des descendants F1 (n = 25) démontraient des décharges myotoniques. Quand les deux parents présentaient des décharges myotoniques, quatre descendants F1 étaient myotoniques et deux non-myotoniques selon l'EMG. L'hérédité ne semble pas liée au sexe. Ces résultats sont plutôt compatibles avec un mode de transmission par un gène autosome à caractère dominant. La paralysie périodique hyperkaliémique et les décharges myotoniques à l'EMG pourraient avoir la même origine. (*Traduit par Dr André Vrins*)

INTRODUCTION

Hyperkalemic periodic paralysis (HPP) was originally described in 1985-86 as the result of the independent efforts of two groups of clinicians (1,2). The condition principally affects Quarter Horses and is characterized by intermittent attacks of muscle fasciculation and spasm. Serum potassium concentrations are elevated during clinical episodes. Between episodes, affected horses usually appear clinically normal, although some may show percussion myotonia (1,3,4-6). To date, the majority of affected horses belong to one blood line. In a recent study of 16 Quarter Horses and one American Paint Horse, all shared one sire, A, as a common ancestor (7). The familial nature of the condition suggests that it may be genetic in origin. In support of this, it was recently reported that breeding an affected stallion with an affected mare resulted in three affected offspring (6). In people a similar condition is inherited as an autosomal dominant trait (8,9).

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The frequency of attacks is quite variable and some horses only develop clinical signs late in life (6). This makes genetic studies difficult because many years can pass before clinical abnormalities are observed. However, we have recently shown that electromyographic examination is consistently abnormal between attacks (10). Other workers report similar conclusions (6). Horses with HPP show signs of spontaneous activity such as fibrillation potentials, positive waves, doublets, myotonic discharges and bizarre high frequency discharges on electromyographic (EMG) examination. Doublets are a very sensitive and specific finding in HPP but require careful analysis of EMG tapes to detect them. Electromyography findings of myotonic discharges were seen in six of seven horses with HPP (10). The electromyographically nonmyotonic HPP affected horse was undergoing diuretic therapy at the time of testing which may have masked this EMG feature of the disease (10). In another study nine horses with HPP showed bizarre high frequency discharges or myotonic discharges on EMG (6). Myotonic and bizarre high frequency discharges are easy to detect on EMG and could therefore be used as a marker to follow the results of mating horses with HPP. The test should enable positive horses to be detected before clinical signs of HPP have been observed.

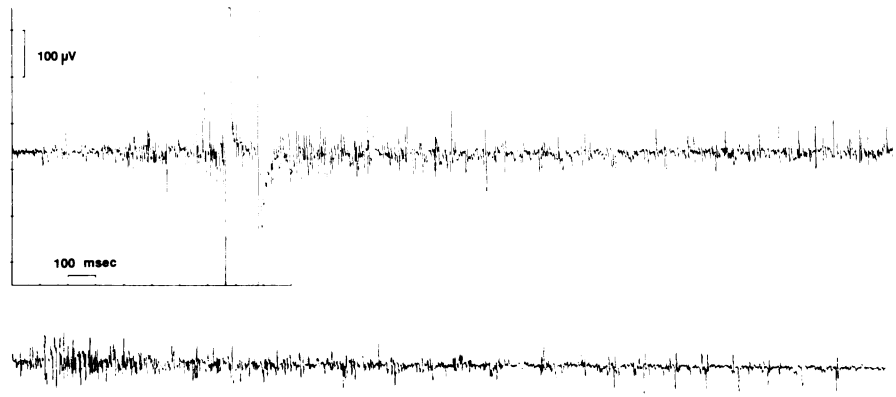

Fig. 1. Myotonic discharge. The bottom trace is a continuation of the top trace.

MATERIALS AND METHODS

ELECTROMYOGRAPHY

A total of five stallions, 16 mares and 40 foals were tested by EMG as previously described (10). The test was performed standing and the horses were restrained either by twitching or by tranquilization with xylazine at 0.5 to 1 mg/kg body weight. Only two horses, stallion HSM and one of his offspring (both showed myotonic discharges on EMG testing) were being treated for HPP at the time of the study. The EMG findings were interpreted without knowledge of each animal's previous clinical history or of their breeding. During the first year of the study EMG's were interpreted as they were performed. In subsequent years the EMG's were recorded on tape and interpreted at a later date without knowledge of the horse's identity. On the basis of this the horses were divided into those that showed EMG evidence of spontaneous activity together with high frequency discharges (>20/s) that lasted for more than 1 s and those that did not. High frequency discharges were either of variable frequency and amplitude and thus were true myotonic discharges (Fig. 1) or were of constant amplitude and frequency and thus were bizarre high frequency discharges (6, 10–12).

IDENTIFICATION OF FARMS

Studies were performed on two cooperating brood mare farms. Farm 1 was identified through a clinical case of HPP in stallion HSM, who was a son of sire A. Farm 2 used horses that were descended from sire A for breeding. However, prior to the commencement of the study no signs of clinical HPP had been seen in horses kept at this farm.

BREEDING STUDIES

Affected (myotonic) horses were defined on the basis of EMG findings of spontaneous activity together with myotonic or bizarre high frequency discharges. Unaffected (nonmyotonic) horses had no myotonic discharges or bizarre high frequency discharges on EMG.

Farm 1 used affected stallion HSM for breeding for a period of six years. The stallion had been confirmed to have HPP on the basis of a high serum potassium during a clinical episode (2). At this farm stallion HSM and mares FSM and JMM were both descended from sire A. At the initial visit, all the breeding animals on the farm, ten mares and stallions HSM and GSN, were tested using EMG. The farm was visited annually for four years, and during this time 32 offspring were tested. All but one of the offspring born to the mares between 1984 and 1989 were tested. Two of seven foals born in 1990 were tested; the untested foals had either been sold or were not halter broken.

Farm 2 had no clinically affected stock. Two stallions, ISN and FSM, and mare IMM, descended from sire A were tested. Additionally, stallion OSN, and five mares, none of which were descended from sire A were tested. Eight F_1 offspring of various matings were also tested.

STATISTICS

Two-tailed Fisher's exact tests were used to determine if the observed ratios were significant. For matings of one parent with myotonic discharges and one electromyographically nonmyotonic parent the expected ratio was 1:1, for matings where both parents showed myotonic discharges the expected ratio was three offspring with myotonic discharges:one offspring with no EMG evidence of myotonic discharges. Both these ratios assume that parents with myotonic discharges were heterozygous for the defect.

RESULTS

Review of EMG tapes yielded results identical with those made at the time EMG was performed.

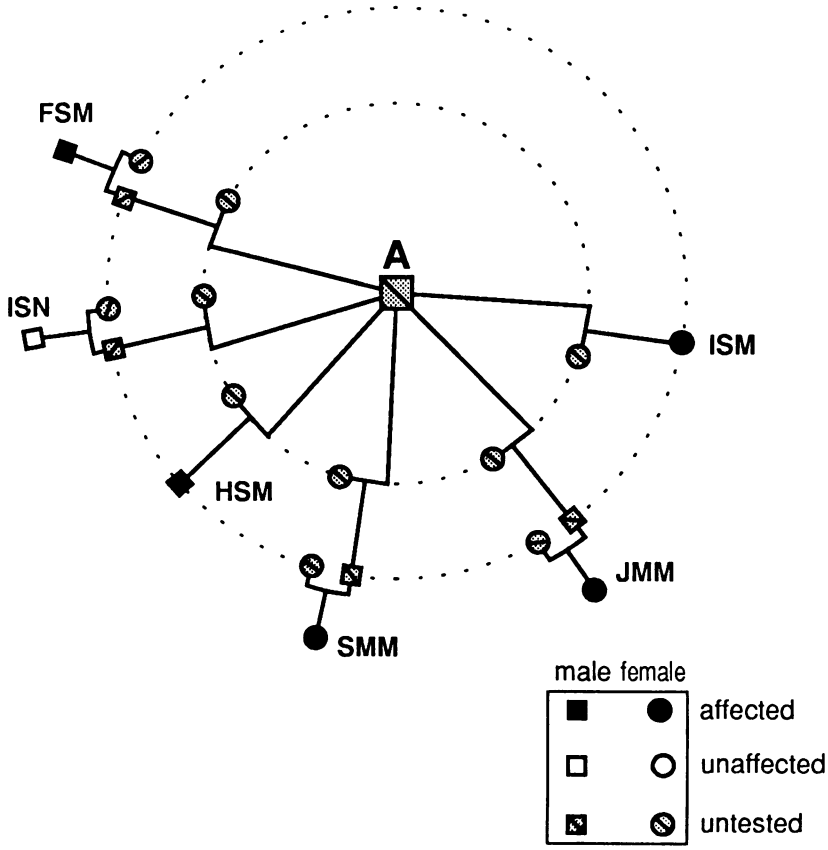

Fig. 2. Interrelationships and presence of myotonic discharges on electromyography in horses descended from sire A. Sire A has been previously implicated as heading a family of Quarter Horses which are predisposed to hyperkalemic periodic paralysis (7).

Of the adult breeding stock (n = 21), which formed the F_0 generation for our trials, six were descended from sire A (Fig. 2). The remaining 15 horses were not closely related, the only breeding horses to share common parents were mares MMN and PMN, which shared a common sire. In addition mare DMN, which was not descended from sire A shared a common dam with sire HSM, which was descended from sire A.

Tests on the F_0 generation indicated that in addition to the previously identified affected stallion HSM (2,10), five adult horses exhibited EMG evidence of myotonic discharges. Of six horses that were first or second generation offspring of sire A, five showed myotonic discharges on EMG (Fig. 2). Of 13 mares and two stallions that did not have sire A as an ancestor, only one showed EMG evidence of myotonic discharges. The positive horse, mare GMM, shared no common ancestor with sire A in the preceding three generations. Fisher's exact test indicated that it was extremely unlikely ($p < 0.001$) that chance accounted for the high incidence of myotonic discharges in horses descended from sire A.

BREEDING STUDIES

Foals only showed electromyographic evidence of myotonic discharges if one or both parents were positive for myotonic discharges on EMG. Myotonic discharges were seen in exactly half of 34 F_1 foals born to matings in which either one or both parents were affected. In comparison there were no affected foals in six offspring born to matings of unaffected mares with unaffected sires. This difference was statistically significant ($p = 0.03$).

Mating electromyographically unaffected stallions with unaffected mares produced unaffected F_1 offspring (Table I).

TABLE I. Results of breeding electromyographically nonmyotonic stallions with electromyographically nonmyotonic mares

		Number of offspring	
Stallion	Mare	Myotonic discharges	No myotonic discharges
GSN	RMN	0	1
GSN	DMN	0	1
ISN	OMN	0	2
ISN	IMN	0	1
OSN	EMN	0	1
Total		0	6

Mating affected stallions HSM and FSM, with affected mares produced both electromyographically myotonic and nonmyotonic offspring in a ratio that was not significantly different ($p > 0.2$) from 3:1 (Table II). One of the two nonmyotonic foals was reexamined a year later. At this time it was still nonmyotonic and showed no spontaneous activity, close examination of a tape of the EMG revealed no evidence of doublets.

TABLE II. Results of breeding electromyographically myotonic to electromyographically myotonic mares

		Number of offspring	
Stallion	Mare	Myotonic discharges	No myotonic discharges
HSM	JMM	0	1
HSM	SMM	3	1
FSM	GMM	1	0
Total		4	2

Mating an affected mare IMM to unaffected stallion ISN resulted in one offspring with no myotonic discharges. Mating an electromyographically affected stallion FSM with nonaffected mares GMN and TMN resulted in one electromyographically nonmyotonic offspring and one offspring with myotonic discharges. Mating an affected stallion with eight unaffected mares resulted in myotonic discharges in half the F_1 offspring, and the ratio of affected to unaffected offspring was not significantly different from 1:1 ($p > 0.2$) (Table III). No evidence of sex linkage was observed; of 12 affected foals four were male and eight were female, this ratio is not significantly different ($p > 0.2$) from 1:1. There were three male and ten female electromyographically nonmyotonic

TABLE III. Results of breeding electromyographically myotonic stallion HSM to eight electromyographically normal mares

Mare	Number of offspring	
	Myotonic discharges	No myotonic discharges
HMN	3[a]	1
KMN	2	2
MMN	3	0
AMN	0	2
RMN	1	4
PMN	2	2
DMN	0	2
SMN	1	0
Total	12	13

[a]Includes filly that was electromyographically nonmyotonic as a foal and myotonic as a two year old

foals, this ratio is not significantly different from 1:1 ($p>0.2$). Overall there was no evidence of an association between myotonic discharges and sex of the F_1 offspring ($p>0.2$).

RELATIONSHIP BETWEEN MYOTONIC DISCHARGES AND CLINICAL SIGNS OF HPP

Spontaneous clinical signs consistent with HPP were only observed on farm 1. A total of six horses showed signs — the affected stallion, and one mare and four foals which had myotonic discharges on EMG. An electromyographically myotonic yearling purchased from farm 2 developed clinical signs of HPP with serum hyperkalemia when challenged with oral potassium chloride at 0.1 g/kg. Clinical signs were not seen in electromyographically nonmyotonic horses.

REPRODUCIBILITY OF EMG FINDINGS

Fourteen horses were tested by EMG on two occasions at least one year apart. Two adults and two foals showed myotonic discharges at both testings, five adults and four foals showed no myotonic discharges at both testings. One foal showed no myotonic discharges as a weanling and myotonic discharges as a two year old.

DISCUSSION

In this study only six of 23 horses with myotonic discharges on EMG showed clinical signs of HPP and it is important to know the relationship between HPP and EMG evidence of myotonia. The fact that clinical signs of HPP were only observed in electromyographically myotonic horses suggests that these two conditions are linked. Furthermore of six breeding stock with myotonic discharges, five were descended from sire A, which had been previously implicated as the head of the line of horses predisposed to HPP (7). A previous study failed to find myotonic discharges in clinically normal Quarter Horses that were not descendants of sire A (10). Reports of myotonic discharges on EMG in horses are rare (13,14). To date HPP is the only condition that has been associated with myotonic discharges in Quarter Horses (1,2,6,10). This suggests that the Quarter Horses with electromyographic evidence of myotonic discharge in this study suffer from the same underlying defect as is present in HPP. To fully confirm this, Quarter Horses with electromyographically demonstrable myotonic discharges should be tested by potassium challenge (1,3) to see if clinical signs of HPP can be induced. This would be particularly interesting in the case of mare GMM, which is the only Quarter Horse with myotonic discharges that was not descended from sire A. The effects of potassium challenge in horses that are electromyographically myotonic or nonmyotonic are currently under investigation.

The low incidence of signs of HPP in horses with myotonic discharges may be because clinical episodes of HPP can be very infrequent. One study reports that an affected horse only showed one clinical attack during a five year period (6). Another reported that the median age of the first attack of HPP was three years (7). Two brood mares with myotonic discharges and most of the offspring in which clinical signs of HPP were not observed, were on the farm for less than two years, so long-term observations were not possible. Furthermore, in a breeding operation horses are often left unattended for long periods of time so brief attacks of HPP might well go unnoticed.

Mating affected dams with affected sires produced four affected and two nonaffected F_1 offspring; this ratio is not significantly different from the 3:1 ratio expected for an autosomal dominant condition but the numbers are too low for confidence in this result. In rare instances horses with HPP fail to show myotonic discharges so the absence of myotonic discharges does not completely rule out the presence of HPP in the nonmyotonic offspring (10). However, one of the nonmyotonic foals was reexamined and still failed to show myotonic discharges, spontaneous activity or doublets. These latter features are reported to be consistently present in HPP affected horses (10). The production of offspring without myotonic discharges or other signs consistent with abnormal muscle function rules out a recessive mode of inheritance.

Breeding an affected parent to an unaffected parent resulted in EMG findings of myotonic discharges in approximately half the offspring (13 myotonic, 15 nonmyotonic on EMG testing). This ratio would be expected if myotonic discharges are the result of an autosomal dominant gene and the affected parent is heterozygous.

The affected F_0 are likely to be heterozygotes because five of six were sired by sire A and probably inherited an allele for HPP from sire A. Affected mare GMM was not related to sire A or to any other affected F_0 parents nor did she share a common ancestor in the preceding three generations with the affected F_0 horses. Of the 15 F_0 parents that were not descended from sire A, only mare GMM was affected on EMG testing. Thus affected horses are rare outside sire A's descendants. Therefore it is unlikely that the affected F_0 sired by stallion A inherited a second allele for HPP from their maternal parents. Furthermore if any of the F_0 were homozygotes and the gene were dominant, then all the offspring of affected F_0 would have been affected.

There was no evidence of sex linkage in this study. Horses of both sexes were affected with myotonic discharges and the ratio of affected males:affected females did not significantly differ from 1:1. If the affected gene was dominant and X linked then all the females born to matings of an affected stallion would be affected. In our study only some of the females of this type of mating were affected. If the affected gene was Y linked then all the males born to an affected stallion

would be expected to be affected. In our study only some of the male F_1 offspring were affected.

Myotonic discharges and HPP are probably different manifestations of the same underlying genetically determined defect in muscle metabolism. This study suggests that myotonic discharges in Quarter Horses are inherited in an autosomal dominant manner. This is consistent with studies of HPP in people which indicate an autosomal dominant mode of inheritance (8,9). This interpretation is consistent with studies of other workers who produced three offspring with HPP by mating a HPP affected mare with a HPP affected stallion (6).

In horses, clinical signs of HPP are more commonly observed in males than females (1,3,7,10). This apparent predilection may be partially the result of differences in observation of mares and stallions. Successful show and breeding stallions are likely to be more closely observed than mares. Another explanation for the predilection for males is that the hormonal milieu may affect muscle development and influence the severity of signs in animals with HPP.

The degree of penetrance of this genetic defect in Quarter Horses depends on the criteria used to define an affected horse. The data presented here and elsewhere (10) suggests that the presence of myotonic discharges is a sensitive indicator of the defect. Clinical signs of HPP were observed rarely. This may be because signs are only rarely expressed and require an appropriate environment — such as a high potassium diet — and careful observation over a long period of time to be detected.

In conclusion these results have important implications for Quarter Horse breeders. Descendants of sire A accounted for 2% of registered Quarter Horses at the end of 1988 (7). The proportion of affected horses in affected generations should decrease due to dilution unless affected horses are selected. It is interesting to note that of six breeding animals which were first or second generation offspring of sire A, five showed myotonic discharges. One would expect only half the first generation offspring of a parent with a dominant trait to be affected, and a quarter of the second generation offspring, so breeders may be unconsciously selecting for affected horses. This may be because horses with HPP are often well muscled (1). Physiologically it is possible that the constant muscle activity associated with myotonic discharges could lead to muscular hypertrophy. The resulting well muscled appearance could favorably impress show judges and breeders.

On the positive side the use of electromyography, coupled with a knowledge of the genetics of the condition, means that it should be relatively easy to greatly reduce the incidence of HPP in the breed by eliminating all EMG positive horses from the breeding pool.

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